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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LE, EMILY M	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 10/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/627,413	KRIEG ET AL.	
	Examiner	Art Unit	
	Emily Le	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 July 2003 and 04 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-71* is/are pending in the application.

4a) Of the above claim(s) *44-46,52-54 and 59-61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-43, 47-51, 55-58 and 62-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/14/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of species 5'TCG3' in the reply filed on 08/04/2006 is acknowledged.

Status of Claims

2. Claims 1-41 are cancelled. Claims 42-71 are added. Claims 44-46, 52-54 and 59-61 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 08/04/2006. Claims 42-43, 47-51, 55-58 and 62-71 are under examination.

Oath/Declaration

3. MPEP 608.04(b) New Matter by Preliminary Amendment [R-3] provides the following:

During examination, if an examiner determines that a preliminary amendment that is present on the filing date of the application includes subject matter not otherwise supported by the originally filed specification and drawings, and the oath or declaration does not refer to the preliminary amendment, the examiner may require the applicant to file a supplemental oath or declaration under 37 CFR 1.67 referring to the preliminary amendment. In response to the requirement, applicant must submit (1) an oath or declaration that refers to the preliminary amendment, (2) an amendment that cancels the subject matter not supported by the originally filed specification and drawings, or (3) a request for reconsideration.

In the instant, a preliminary amendment is present on the filing date of the instant patent application that includes subject matter that may not otherwise be supported by the originally filed specification and drawings, and the oath or declaration does not refer to the preliminary amendment. To safeguard Applicant, particularly from the requirement implied in the oath or declaration whereby the inventor is required to review and understand the contents of the application, and acknowledge the duty to disclose to the Office all information known to be material to patentability as defined by 37 CFR 1.56, Applicant is required to submit a supplemental oath or declaration under 37 CFR 1.67 referring to the preliminary amendment. Failure to submit a supplemental oath or declaration under 37 CFR 1.67 referring to a preliminary amendment that contains subject matter not otherwise included in the specification or drawings of the application as filed removes safeguards that are implied in the oath or declaration requirements that the inventor review and understand the contents of the application, and acknowledge the duty to disclose to the Office all information known to be material to patentability as defined in 37 CFR 1.56.

Information Disclosure Statement

4. The Information Disclosure Statement (IDS) filed 01/14/2004 has not been fully considered for the following reasons:

37 CFR 1.56(b) states that information is material to patentability when it is **not cumulative** to information already of record or being made of record in the application, and (1) **It establishes, by itself or in combination with other information, a prima facie case of unpatentability of a claim**; or (2) It **refutes, or is inconsistent with, a**

position the applicant takes in: (i) Opposing an argument of unpatentability relied on by the Office, or (ii) Asserting an argument of patentability. [Emphasis added] A prima facie case of unpatentability is established when the information compels a conclusion that a claim is unpatentable under the preponderance of evidence, burden-of-proof standard, giving each term in the claim its broadest reasonable construction consistent with the specification, and before any consideration is given to evidence which may be submitted in an attempt to establish a contrary conclusion of patentability. It is incumbent upon patent applicants, therefore, to bring "material" information to the attention of the Office.

In the instant, a review of the all of the 46 U.S. Patent and PreGrant Patent documents listed in the IDS, among a total of more than 200 references cited, the Office finds that the information provided in the references do not compel a conclusion that a claim is unpatentable. In view of the very low percentage of references material to patentability in the sampled documents reviewed, the submission is not in compliance with 37 CFR 1.56 and 1.98. Accordingly, the remaining references will not be considered. Thus, the Information Disclosure Statement filed has not been fully considered.

Additionally, the information disclosure statement filed is not in full compliance with the requirements of 37 C.F.R 1.98 (b) (5), which requires: Each publication listed in an information disclosure statement must be identified by publisher, author (if any), title, relevant pages of the publication, date, and place of publication.

MPEP § 609.04 (a) [R-3] (I) provides that the date of publication supplied must include at least the month and year of publication, except that the year of publication (without the month) will be accepted if the applicant points out in the information disclosure statement that the year of publication is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the particular month of publication is not in issue.

In the instant, neither the publisher is provided for each of the non-patent publications listed on the IDS nor is the date of publication provided in accordance with the guideline(s) set forth in MPEP § 609.04 (a) [R-3] (I). Hence, the IDS submitted fails to comply with the requirements of 37 C.F.R 1.98. Thus, the rest of the IDS has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

6. Claims 42-43, 47-51, 55-58 and 62-71 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is directed toward a method of treating, preventing and ameliorating papilloma viral infection with the administration of an oligonucleotide comprising at least one unmethylated CpG motif to a subject having papilloma viral infection.

The basic inquiry for possession is: Can one skilled in the art reasonably conclude that the inventor was in possession of the claimed invention at the time the application was filed? If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, *even if every nuance of the claim is not explicitly described in the specification*, then the requirement for an adequate written description is met.

To provide adequate written description and evidence of possession, the specification must provide sufficient description of the claimed invention by i) actual reduction to practice, ii) reduction to drawings; or iii) disclosure of relevant identifying characteristics, such as disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, correlation between structure and function, and methods of making the claimed invention. The analysis:

i) Sufficient description of the claimed invention by actual reduction to

practice: The only instance in which the specification refers to papilloma viral infection is on Line 21, page 14, wherein the specification lists papilloma viruses as one of the many examples of infectious virus. Beside that single reference to papilloma viruses, the specification does not teach anything else relating to papilloma viral infection and the use of an oligonucleotide comprising the CpG motif to treat, prevent or ameliorate the infection. Not a single oligonucleotide containing the CpG motif that treats, prevents or ameliorates papilloma viral infection is provided in the specification. In the instant, the disclosure fails to evidence that Applicant is in possession of the claimed invention by actual reduction to practice.

ii) Sufficient description of the claimed invention by reduction to drawings: The instant patent application is filed with many drawings. However, none of the drawings provided sets forth an oligonucleotide comprising the CpG motif that treats, prevents or ameliorate any viral infection, including papilloma viral infection. Hence, the disclosure fails to evidence that Applicant is in possession of the claimed invention by reduction to drawings.

iii) iii) disclosure of relevant identifying characteristics: The disclosure fails to provide relevant identifying characteristics relating to the claimed invention. The disclosure fails to set forth the complete structure of an oligonucleotide that treats, prevents or ameliorate papilloma viral

infection. The disclosure does not even set forth the partial structure of oligonucleotides containing the CpG motif that treat, prevent or ameliorate papilloma viral infection. The disclosure further failed to set forth the physical and chemical properties of oligonucleotides encompassed by the claimed invention. Furthermore, the disclosure failed to set forth any functional characteristics that oligonucleotides containing the CpG motif must possess to treat, prevent or ameliorate papilloma viral infection.

In the instant, nothing exists in the specification to demonstrate that Applicant is in possession of an oligonucleotide containing the CpG motif that treats, prevents and ameliorate any viral infection, including papilloma viral infection. In the absence of any evidence demonstrating that Applicant is in possession of the primary active ingredient for the claimed invention, oligonucleotides comprising the CpG motif that treat, prevent or ameliorate papilloma viral infection, the skilled artisan cannot reasonably conclude or recognize that Applicant is in possession of the claimed invention at the time the invention was filed.

Applicant is reminded that that written description requirement is separate and distinct from the enablement requirement.

7. Claims 42-43, 47-51, 55-58 and 62-71 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In Genentech *Inc. v. Novo Nordisk* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also *Amgen Inc. v. Chugai Pharm. Co.,* 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); *In re Fisher* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Further, in *In re Wands* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman* [230 USPQ 546, 547 (Bd Pat App Int 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Breadth of the claims:

The claimed method of treating, preventing or ameliorating papilloma viral infection in a subject with the administration of an oligonucleotide comprising at least one unmethylated CpG motif to the subject.

The specification provides the following, A "subject" shall mean human or vertebrate animal including a dog, cat, horse, cow, pig, sheep, goat, chicken, monkey, rat, and mouse. [Lines 31-32, page 19.]

Hence, the breadth of the claims is directed to a method of treating, preventing or ameliorating papilloma viral infection in a subject with the administration of an oligonucleotide comprising at least one unmethylated CpG motif to the subject. The subjects encompassed by the claimed invention are all vertebrate animals, including humans.

Presence or Absence of working examples:

The specification does not contain any working examples that are directed to the claimed invention, a method of treating, preventing or ameliorating papilloma viral infection in a subject with the administration of an oligonucleotide comprising the CpG motif. The specification does not containing any working examples demonstrating that such oligonucleotides treat, prevent or ameliorate any viral infection. Nothing exists in the specification demonstrating that fundamental research has been conducted to support Applicant's claimed invention, wherein oligonucleotides comprising the CpG motif treat, prevent or ameliorate viral infection, including papilloma viral infection.

Amount of direction or guidance present in the specification:

The specification only refers to papilloma virus once, line 21, page 14. Beside this single reference to the virus, the specification does not contain any teachings relating to the virus. In the instant, the specification does not set forth any evidence demonstrating that oligonucleotides containing the CpG motif treat, prevent or ameliorate viral infection. All that is present in the specification are conjectures of potential application of such oligonucleotides in the treatment, prevention and

amelioration of viral infections in vertebrate subjects. However, none of these conjectures are substantiated by any evidence.

Nature of the invention

Based on Applicant's disclosure, it appears that the nature of the claimed invention is directed to the use of the art recognized immunostimulatory activity of oligonucleotides containing the CpG motif, including the induction of Th1 immune response invoked by the production of Th1 associated cytokines, accorded by the CpG motif, to render a therapeutic value, wherein the desired therapeutic value is to provide treatment, prevention and amelioration of papilloma viral infection in vertebrate subject--immunotherapy.

State of the Art:

In the instant, the involvement of a Th1 type immune response in combating against intracellular pathogens is a well-recognized general concept. The art acknowledges the importance of Th1 type immune response, which is stimulated by the production of Th1 associated cytokines, in the elimination of intracellular pathogens, including viruses. However, the art has not accredited or recognized any one particular Th1-associated cytokine to the treatment, prevention and amelioration of viral infection in a subject. Specifically, the art teaches that while cytokines secreted by T helper cells are of critical importance for the outcome of many infectious diseases, the production of the "right" set of cytokines can be a matter of life or death, as noted by Infante-Duarte et al. Infante-Duarte et al. further notes that in addition to a Th1 type immune response, a Th2 type immune response is also necessary. Specifically, Infante-Duarte et al.

teaches that a tight control over where and when Th1 and Th2 immune responses happen is necessary to keep intracellular infections under control, and to prevent the Th1 type immune response from causing damage to the host.[1] Hence, while the importance of a Th1 type immune response is well recognized in the art, the art further notes that a balance between Th1 and Th2 type immune responses is necessary to resolve an infection.

The cytokine art also provides that the efficacy of Th1 associated cytokines, such as interleukin 2, interleukin 12 and interleukin 18, against intracellular pathogens are controversial, as evidenced by Aoki et al.,[2] Bohn et al.,[3] Sakao et al.,[4] Zaitseva et al.,[5] and Masihi, K.[6]. Aoki et al. teaches that while interleukin 2 may confer good protection for non-pathogenic mycobacterial strain Bacille Calmette-Guerin (BCG), interleukin 2 does not confer protection for virulent *M. bovis* infection. Bohn et al. teaches that interleukin-12, a Th1 associated cytokine, induces different effector mechanisms that result in either protection or exacerbation of a disease. Specifically, Bohn et al. notes that the administration of exogenous interleukin 12 confers protection against Yersinia enterocolitica in susceptible BALB/c mice, but exacerbates yersiniosis in resistant C57BL/6 mice. Sakao et al. teaches that interleukin 18, a Th1 associated cytokine, is

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[1] Infante-Duarte et al., Th1/Th2 balance in infection. Springer Seminars in Immunopathology, 1999, 21: 317-338. [Paragraph bridging pages 321-322, in particular.]
[2] Aoki et al. Use of cytokines in infection. Expert Opin. Emerg. Drugs, 2004, vol. 9, No. 2, 223-236. [Lines 4-15, left column, page 229,in particular]
[3] Bohn et al., Ambiguous role of interleukin-12 in Yersinia enterocolitica infection in susceptible and resistant mouse strains. Infect. Immune., 1998, Vol. 66, 2213-2220. [Abstract, in particular.]
[4] Sakao et al. IL-18-deficient mice are resistant to endotoxin-induced liver injury but highly susceptible to endotoxin shock. Int. Immunol., 1999, Vol. 11, 471-480. [Abstract, in particular.]
[5] Zaitseva et al. Interferon gamma and interleukin 6 modulate the susceptibility of macrophages to human immunodeficiency virus type 1 infection. Blood, 2000, Vol. 96, 3109-3117. [Abstract, in particular]

responsible for the progression of endotoxin-induced liver injury in mice primed with interleukin 18. Zaitseva et al. teaches that both interleukin 6 and interferon gamma augment the susceptibility of monocyte-derived macrophages to infection. Masihi, K. notes that interleukin 2 increases the production of HIV in vitro, and enhances the translocation of bacteria from intestines to other organs in animal studies. In summation, the art teaches that cytokines can be inherently toxic, have unclear pharmacological behavior and also have pleiotropic effects. Hence, the art recognizes that the use of cytokine to direct treatment is unpredictable and complicated.

Additionally, while the art teaches that oligonucleotides containing the CpG motif are capable of stimulating a Th1 type immune response, however, the art also teaches that the Th1 associated cytokine profile for these oligonucleotides vary from one oligonucleotide and species of subject to the next, as evidenced by Krieg et al.[7] and Mutwiri et al.[8] Krieg et al notes that each oligonucleotide containing the CpG motif must be considered as a separate agent because the quality and type of immune stimulation induced by these oligonucleotides varies. Krieg et al. particularly notes that the type of cytokine stimulated by oligonucleotides containing the CpG motif is distinct from one oligonucleotide to the next. Additionally, both Krieg et al. and Mutwiri et al. note that the level and type of immune stimulation varies depending on i) the specific nucleic acids, purines and pyrimidines, surrounding the CpG motif; ii) the spacings

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[6] Masihi, K. Fighting infection using immunomodulatory agents. Expert Opin. Biol. Ther., 2001, Vol. 1, No. 4, 641-653. [Lines 15-25, left column of page 646, in particular]
[7] Krieg et al., CpG motif in bacterial DNA and their immune effects. Annu. Rev. Immunol., 2002, Vol. 20, 709-760. [paragraph that bridge pages 716-717, in particular.]

between CpG motifs; iii) the numbers of CpG motifs in an oligonucleotide; iv) the absence or presence of a CpG motif to the end of the oligonucleotide; and v) the context in which the CpG motif is presented in the sequence.

The CpG art further teaches that the immunostimulatory activity of oligonucleotides containing the CpG is very species specific, as evidenced by Mutwiri et al. Table 1 of Mutwiri et al. provides that the *in vitro* immunostimulatory activity of oligonucleotides containing the CpG motif varies from one species to the next. Mutwiri et al. also notes that the level of immunostimulating induced by a particular oligonucleotide is also dependent on the sequence(s) flanking the CpG motif. Specifically, Mutwiri et al. notes that the GTCGTT motif, which is the optimal motif for humans, is optimal for stimulation of lymphocyte proliferation in several species including cattle, sheep, goats, horses, pigs, dogs, cats and chickens; whereas the murine CpG motif (GACGTT) is only optimal for inbred rabbits and mice.

Furthermore, both Krieg et al. and Mutwiri et al. sets forth that the recognition of the CpG motifs requires Toll-like receptor (TLR) 9, wherein cells that express TLR-9 produce Th1 associated cytokines. However, Mutwiri et al. provides that TLR-9 has only been identified in mice and humans. Mutwiri et al. also provides that the TLR-9 is differentially expressed in humans and mice. Hence, if the recognition of the CpG motif were dependent of TLR-9, then it would logically follows that the extent of the Th1 type immune response induced by the oligonucleotide would necessarily vary from one

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[8] Mutwiri et al. Biological activity of immunostimulatory CpG DNA motifs in domestic animals. Veterinary Immunology and Immunopathology, 2003, Vol. 91, 89-103. [See 2nd and 3rd full paragraphs, left column of page 93; last sentence of paragraph bridging pages 89-90.]

species to the next. Mutwiri et al. also sets forth that *in vitro* observations do not accurately predict what happens *in vivo*.

Moreover, the potential use of oligonucleotides containing the CpG motif to stimulate a Th1 type immune response that treats and prevents infection is widely speculated in the art. However, efforts to harness the immunostimulatory activity of oligonucleotides containing the CpG motif to trigger an innate immune response that protect a host from infectious pathogen has proven to be challenging and elusive, as evidenced by Yamamoto et al.,[9] Equils et al.,[10] Agrawal et al.,[11] and Olbrich et al.[12] Yamamoto et al. reports that oligonucleotides containing the CpG motif failed to improve the survival in mice challenged with influenza. Equils et al. teaches that such oligonucleotides can induce the HIV transcriptional regulatory elements in long terminal repeats, increasing viral replication. Agrawal et al. teaches that HIV-infected humans treated with oligonucleotides containing the CpG motif showed dose-dependent increases viral load. Lastly, Olbrich et al. teaches that the administration of oligonucleotides containing the CpG motif accelerated and increased the severity of Friend retrovirus in mice. In the case of Olbrich et al., the author notes that the use of oligonucleotides containing the CpG motif for the treatment of viral infection may be a double edge sword that can resolute in effective therapy but also in acceleration of

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[9] Yamamoto et al., Oligodeoxyribonucleotides with 5'ACGT-3' or 5TCGA-3 sequence induce production of interferons. Curr. Top. Microbiol. Immunol. 2000, Vol. 247, 23-40.
[10] Equils et al. Toll-like receptor 2 (TLR2) and TLR9 signaling resulted from HIV-long terminal repeat transactivation and HIV replication in HIV-1 transgenic mouse spleen cells: implications of simultaneous activation of TLRs on HIV replication. J. Immunol. 2003, 170, 5159-5164.
[11] Agrawal, et al. Was induction of HIV1 through TLR9? J. Immunol. 2003, 171, 1621-1621.
[12] Olbrich et al. Preinfection treatment of resistant mice with CpG oligodeoxynucleotides renders them susceptible to friend retrovirus-induced leukemia. J. Virol., 2003, 77, 10658-10662.

disease. Olbrich et al. notes that this double edge sword observation may be dependent on the time point of treatment.

Hence, overall, the literature notes the use of CpG to stimulate the production of cytokines, the use of cytokines to influence viral infection, and the development of a treatment regimen for diseases is unpredictable and complicated.

Additionally, the papilloma viral art also notes the failure of oligonucleotides comprising the CpG motif to demonstrate any therapeutic effect on papilloma growth, as evidenced by Poetker et al.[13] Poetker et al. also notes that the lack of a therapeutic effect by the oligonucleotide suggests that either enhanced papilloma antigen presentation or targeting of immune evasive mechanisms used by the papillomas is needed to treat bulky disease with an immunotherapeutic strategy. And Poetker et al. further notes that such mechanism will need to be addressed if immunotherapeutic strategies are to be rationally and successfully applied. In the instant, while the claimed invention utilizes immunotherapeutic approach, it is noted that the immunotherapeutic strategy does not include an enhanced papilloma antigen presentation or targeting of immune evasive mechanisms used by the papillomas. None of these factors are present in the claimed invention.

Predictability or unpredictability of the art:

As discussed above, the art recognizes that the use of cytokine to direct treatment is unpredictable and complicated. The art also recognizes that use of CpG to stimulate cytokine production, the use of the induced cytokine to influence viral

infection, and the development of treatment regimen unpredictable and complicated. The art additionally teaches that the efforts to harness the immunostimulatory activity of oligonucleotides containing the CpG motif to trigger an innate immune response that protect a host from infectious pathogen has proven to be challenging and elusive.

Quantity of experimentation necessary:

Extreme undue burden of experimentation would be imposed upon the skilled artisan practicing the claimed invention. As stated above, Applicant has not provided much, if any, guidance or direction relating to the claimed invention. All that Applicant has provided is a conclusion that is made on the basis of generalized concepts that are well known in the art. And the formation of a conclusion based on generalized concepts renders the conclusion flawed. Generalized concepts are directed to support a general direction of studies or research; however, they do not support concrete conclusions. Concrete conclusions must be substantiated by facts, including evidence. In the instant, while the general direction of research may be outlined for the skilled artisan, the skilled artisan would not readily be able to practice the claimed invention without the undue burden of experimentation. The path that the skilled artisan must take in his research is marked with many challenges that are recognized in the art, including the complex nature of oligonucleotides containing CpG motif and the complexity of the immune system, including the Th1 type immune response and the functional characteristics of its associated cytokines. Hence, in view of the lack of any guidance in the specification concerning the effective use of oligonucleotides to treat, prevent or ameliorate viral

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[13] Poetker et al. Immune Stimulation for the treatment of papilloma. Annals of Otology: Rhinology &

infection in a subject; the unpredictability of oligonucleotides containing CpG motif to stimulate specific immune response; and the inherent toxicity, the unclear pharmacological behavior, and the pleiotropic effects of cytokines; the skilled artisan would not be able to reasonably practice the claimed invention without an undue burden experimentation. Thus, the claims are rejected under 35 U.S.C § 112, 1st paragraph for failing to comply with the enablement requirement.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F. 2d 1557, 1562, 27 USPQ 2d 1510, 1513 (Fed. Cir. 1993).

Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29

USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 42-43, 47-51, 55-58 and 62-71 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 97, of copending Application No. 10/613524.

Claims 42-43, 47-51, 55-58 and 62-71 are directed toward a method of treating, preventing and ameliorating papilloma viral infection with the administration of an oligonucleotide comprising at least one unmethylated CpG motif to a subject having papilloma viral infection.

Claim 97 of the conflicting patent application is directed at a method for preventing a disease in a subject with the administration of an oligonucleotide comprising the CpG.

The difference between the claims is: Claim 97 of the conflicting patent application is not limited to the prevention of papilloma viral infection in a subject. However, it is noted that by "disease", the conflicting patent application also intends to encompass infectious diseases. [See claim 40 of the conflicting patent application] Thus, by the term "disease", the conflicting patent application intends to encompass infectious disease. And the specification, paragraph 22 of the PreGrant publication, of the conflicting application discloses papilloma viral infection as an infectious disease. Thus, by disease, claim 97 of the conflicting patent application also encompasses papilloma viral infection, which is an infectious disease.

The other difference between the claims is: claim 97 of the conflicting patent application is directed to specific species of oligonucleotide, SEQ ID NO: 1, whereas, the claims of the instant patent application is directed to a genus of oligonucleotides. In the instant, the species of oligonucleotide recited in claim 97 of the conflicting patent application is encompassed by the genus of oligonucleotides recited in the claims of the instant patent application. Hence, the species of oligonucleotide recited in claim 97 of the conflicting patent application anticipates the genus of oligonucleotides recited in the claims of the instant patent application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

10. Claims 42-43, 47-51, 55-58 and 62-71 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 37, of copending Application No. 10/894862.

Claims 42-43, 47-51, 55-58 and 62-71 are directed toward a method of treating, preventing and ameliorating papilloma viral infection with the administration of an oligonucleotide comprising at least one unmethylated CpG motif to a subject having papilloma viral infection.

Claim 37 of the conflicting patent application is directed at a method of treating an infection in a subject with the administration of an oligonucleotide comprising the CpG.

The difference between the claims is: claim 37 of the conflicting patent application is not limited to the treatment of papilloma viral infection in a subject. However, it is noted that by "infection", claim 37 of the conflicting patent application includes viral infection. And paragraph 49 of the conflicting patent application's PreGrant publication provides papilloma viral infection as a viral infection. Hence, by infection, claim 37 of the conflicting patent application also encompasses papilloma viral infection.

The other difference between the claims is: claim 37 of the conflicting patent application is directed to a species of oligonucleotide, whereas, the claims of the instant patent application is directed to a genus of oligonucleotides. In the instant, the species of oligonucleotide recited in claim 37 of the conflicting patent application is encompassed by the genus of oligonucleotides recited in the claims of the instant patent application. Hence, the species of oligonucleotide recited in claim 37 of the conflicting patent application anticipates the genus of oligonucleotides recited in the claims of the instant patent application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

11. Claims 42-43, 47-51, 55-58 and 62-71 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 19, of copending Application No. 10/987146.

Claims 42-43, 47-51, 55-58 and 62-71 are directed toward a method of treating, preventing and ameliorating papilloma viral infection with the administration of an oligonucleotide comprising at least one unmethylated CpG motif to a subject having papilloma viral infection.

Claim 37 of the conflicting patent application is directed at a method of treating viral infection in a subject with the administration of an oligonucleotide comprising the CpG.

The difference between the claims is: claim 19 of the conflicting patent application is not limited to the treatment of papilloma viral infection in a subject. However, paragraph 49 of the conflicting patent application's PreGrant publication provides papilloma viral infection as a viral infection. Hence, by viral infection, claim 19 of the conflicting patent application also encompasses papilloma viral infection.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

12. Claims 42-43, 47-51, 55-58 and 62-71 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 42, of copending Application No. 10/382822.

Claims 42-43, 47-51, 55-58 and 62-71 are directed toward a method of treating, preventing and ameliorating papilloma viral infection with the administration of an oligonucleotide comprising at least one unmethylated CpG motif to a subject having papilloma viral infection.

Claim 42 of the conflicting patent application is directed at a method of treating, preventing and ameliorating viral infection in a subject with the administration of an oligonucleotide comprising the CpG.

The difference between the claims is: claim 42 of the conflicting patent application is not limited to the treatment of papilloma viral infection in a subject. However, paragraph 49 of the conflicting patent application's PreGrant publication provides papilloma viral infection as a viral infection. Hence, by viral infection, claim 42 of the conflicting patent application also encompasses papilloma viral infection.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

13. Claims 42-43, 47-51, 55-58 and 62-71 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 59, of copending Application No. 11/255100.

Claims 42-43, 47-51, 55-58 and 62-71 are directed toward a method of treating, preventing and ameliorating papilloma viral infection with the administration of an oligonucleotide comprising at least one unmethylated CpG motif to a subject having papilloma viral infection.

Claim 59 of the conflicting patent application is directed at a method for treating an infectious disease in a subject with the administration of an oligonucleotide comprising the CpG.

The difference between the claims is: Claim 59 of the conflicting patent application is not limited to the treatment of papilloma viral infection in a subject. However, it is noted that by "infectious disease", the conflicting patent application also intends to encompass viral infection. [See claim 60 of the conflicting patent application] Thus, by the term "infectious disease", the conflicting patent application intends to encompass viral infection. And the specification, paragraph 59 of the PreGrant publication, of the conflicting application discloses papilloma viral infection as an infectious disease. Thus, by infectious disease, claim 59 of the conflicting patent application also encompasses papilloma viral infection.

The other difference between the claims is: claim 59 of the conflicting patent application is directed to specific species of oligonucleotide, whereas, the claims of the instant patent application is directed to a genus of oligonucleotides. In the instant, the species of oligonucleotide recited in claim 59 of the conflicting patent application is encompassed by the genus of oligonucleotides recited in the claims of the instant patent application. Hence, the species of oligonucleotide recited in claim 59 of the conflicting patent application anticipates the genus of oligonucleotides recited in the claims of the instant patent application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

14. Claims 42-43, 47-51, 55-58 and 62-71 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 45, of copending Application No. 11/361313.

Claims 42-43, 47-51, 55-58 and 62-71 are directed toward a method of treating, preventing and ameliorating papilloma viral infection with the administration of an oligonucleotide comprising at least one unmethylated CpG motif to a subject having papilloma viral infection.

Claim 45 of the conflicting patent application is directed at a method for treating an infectious disease in a subject with the administration of an oligonucleotide comprising the CpG.

The difference between the claims is: Claim 45 of the conflicting patent application is not limited to the treatment of papilloma viral infection in a subject. However, it is noted that by the term "infectious disease", the conflicting patent application intends to encompass viral infection. [Paragraph 39 of the PreGrant publication of the conflicting application] At the cited passage, the specification of the conflicting patent application discloses papilloma viral infection as an infectious disease. Thus, by infectious disease, claim 45 of the conflicting patent application also encompasses papilloma viral infection.

The other difference between the claims is: claim 45 of the conflicting patent application is directed to specific species of oligonucleotide, whereas, the claims of the instant patent application is directed to a genus of oligonucleotides. In the instant, the species of oligonucleotide recited in claim 45 of the conflicting patent application is

encompassed by the genus of oligonucleotides recited in the claims of the instant patent application. Hence, the species of oligonucleotide recited in claim 45 of the conflicting patent application anticipates the genus of oligonucleotides recited in the claims of the instant patent application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Some of the above rejection are, in part, based on the specification of the conflicting patent application, rather than the claims. In support of the use of this material, the examiner notes the following excerpt from MPEP section 804 II(B)(1):

> When considering whether the invention defined in a claim of an application is an obvious variation of the invention defined in the claim of a patent, the disclosure of the patent may not be used as prior art. This does not mean that one is precluded from all use of the patent disclosure.

The specification can always be used as a dictionary to learn the meaning of a term in the patent claim. In re Boylan, 392 F.2d 1017, 157 USPQ 370 (CCPA 1968). Further, those portions of the specification which provide support for the patent claims may also be examined and considered when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent. In re Vogel, 422 F.2d 438, 441-42, 164 USPQ 619, 622 (CCPA 1970). The court in Vogel recognized "that it is most difficult, if not meaningless, to try to say what is or is not an obvious variation of a claim," but that one can judge whether or not the invention claimed in an application is an obvious variation of an embodiment disclosed in the patent which provides support for the patent claim. According to the court, one must first "determine how much of the patent disclosure pertains to the invention claimed in the

patent" because only "[t]his portion of the specification supports the patent claims and may be considered." The court pointed out that "this use of the disclosure is not in contravention of the cases forbidding its use as prior art, nor is it applying the patent as a reference under 35 U.S.C. 103, since only the disclosure of the invention claimed in the patent may be examined."

Thus, the courts have held that it is permissible to use the specification in determining what is included in, and obvious from, the invention defined by the claim on which the rejection is based. This is true even where elements are drawn from the specification describing the claimed invention which are not elements in the claim itself.

Conclusion

15. No claims allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Le whose telephone number is (571) 272 0903. The examiner can normally be reached on Monday - Friday, 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce R. Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Emily Le 12/4/06
Patent Examiner
Art Unit 1648